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TITLE: 4-Aminobiphenyl (4-ABP)-DNA Damage in Breast Tissue and Relationship to p53 Mutation and Polymorphisms of Metabolizing Genes

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The proposed research project investigates the relationship between environmental exposures and genetic susceptibility factors. This project determined the level of 4-aminobiphenyl(ABP)-DNA adduct levels with immunhistochemical staining in 150 determined by PCR-RFLP. The association between 4-ABP-DNA adduct levels and the carcinogen metabolizing genes CYP1A2, NAT2, NAT1 and GSTP1 were examined. Another aim of this project is to determine if exposure to 4-ABP and its metabolites can cause mutations in the p53 gene. The elucidation of the mutational spectra of p53 for all 150 samples is currently under investigation.

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4-ABP-DNA adducts

The immunohistochemical analysis of 4-ABP-DNA adducts in breast tumor tissue was completed last year. This year the analysis of normal adjacent tissue was determined and a more extensive statistical analysis was completed. Analysis included determining the differences of adduct levels in normal adjacent breast tissue between smokers and nonsmokers. Associations were also determined between 4-ABP-DNA adduct levels and the smoking status variables; pack-years, age at initiation, and smoking intensity.

Genotyping

The determination of CYP1A2 and NAT2 polymorphisms were completed this year by PCR-RFLP. The Fluorescence Polarization-dye-terminator incorporation assay was abandoned due extremely sensitive nature of the assay and the poor quality of DNA acquired from paraffin-embedded tissue. Genotyping of NAT1 and GSTP1 were also completed this year by PCR-RFLP. The statistical analysis to determine the correlations between genotype and adduct levels in both tumor and normal adjacent tissue has been completed.

P53 Mutational Spectra

Difficulties arose in obtaining a difference in band migration between the positive and negative controls on the SSCP polyacrylamide gels. This obsolete method has been deserted for the more efficient and comprehensive p53 GeneChip method. The p53 GeneChip probes are commercially available from Affymetrix. The Cancer Core Facility at Columbia University has an Affymetrix Instrument System available to analyze the GeneChips. Complete sequence data for exons 2-11 in p53 will be determined for the 150 samples. Correlations will be made between identified p53 mutations and 4-ABP-DNA adducts.

Key Research Accomplishments

- Determined that the 4-ABP-DNA adduct levels in normal adjacent breast tissue is slightly elevated, though not statistically significant, in nonsmokers compared to smokers.
- Determined the 4-ABP-DNA adduct levels in tumor tissue were slightly elevated, though modest and not statistically significant, in smokers with higher exposure in relation to pack-years.
- There were no statistically significant differences in 4-ABP-DNA adduct levels in either tumor or normal adjacent tissue between smokers stratified by age at initiation.
- The relationship between the genotypes for the carcinogen metabolizing enzymes, CYP1A2, NAT2, NAT1 and GSTM1 have in predicting 4-ABP-DNA adduct levels was determined. None of these genes, independently or in combination, had a significant association with adduct levels.
- The analysis of the mutational spectra of p53 is currently under investigation.